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ISCHAEMIC HEART DISEASE

The return of CABG over PCI? ► Clinical trials comparing coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) with stents suggest no difference in most patients with significant disease in two or three vessels in the important outcomes of death and recurrent myocardial infarctions. Registry data provides information on larger cohorts of real life patients. New York's cardiac registries identified 37 212 patients with multivessel disease who underwent CABG and 22 102 patients with multivessel disease who underwent PCI from 1 January 1997 to 31 December 2000. The rates of death and subsequent revascularisation within three years after the procedure in various groups of patients according to the number of diseased vessels and the presence or absence of involvement of the left anterior descending (LAD) coronary artery were assessed. Risk adjusted survival rates were significantly higher among patients who underwent CABG than among those who received a stent in all of the anatomical subgroups studied. For example, the adjusted hazard ratio (HR) for the long term risk of death after CABG relative to stent implantation was 0.64 (95% confidence interval (CI) 0.56 to 0.74) for patients with three vessel disease with involvement of the LAD coronary artery and 0.76 (95% CI 0.60 to 0.96) for patients with two vessel disease with involvement of the non-proximal LAD coronary artery. Since it is registry data, with patients assigned to groups by clinicians assessing relative benefits, perhaps the unadjusted analysis—which shows that surgery is only better in three vessel disease with proximal LAD disease—is more valid. This study raises questions about how cardiologists should advise patients.

▲ Hannan EL, Racz MJ, Walford G, *et al*. Long-term outcomes of coronary-artery bypass grafting versus stent implantation. *N Engl J Med* 2005;**352**:2174–83.

Nicotine patches for free increase quit rates ► New York has an aggressive anti-smoking policy. After legislation and increased taxes, a six month study of providing free nicotine replacement therapy (NRT) patches suggests that quit rates are increased at a cost of about £300 per quit. From 34 090 eligible smokers (5% of all smokers in New York) who phoned a toll-free quitline and were sent a six week course of nicotine patches (two weeks each of 21 mg, 14 mg, and 7 mg per day), smoking status of 1305 randomly sampled NRT recipients was compared to a non-randomly selected comparison group of eligible smokers who, because of mailing errors, did not receive the treatment. Of individuals contacted at six months, more NRT recipients than comparison group members successfully quit smoking (33% *v* 6%, $p < 0.0001$), and this difference remained significant after adjustment for demographic factors and amount smoked (odds ratio (OR) 8.8, 95% CI 4.4 to 17.8). Those who received a counselling call were more likely to stop smoking than those who did not (246 (38%) *v* 189 (27%), $p = 0.001$).

▲ Miller N, Frieden TR, Liu SY, *et al*. Effectiveness of a large-scale distribution programme of free nicotine patches: a prospective evaluation. *Lancet* 2005;**365**:1849–54.

Theophylline to prevent contrast nephropathy: the jury is still out ► Nine randomised controlled trials involving 585 patients were identified and included for meta-analysis. Theophylline protocols and definitions of contrast induced nephropathy (CIN) varied across studies. There was evidence of heterogeneity of results across trials ($Q = 9.77$; $p = 0.08$); therefore, pooled values require cautious interpretation. The overall pooled OR using a conservative random effects model was 0.40 (95% CI 0.14 to 1.16; $p = 0.09$) indicating a trend toward reduction in the incidence of CIN with theophylline use. The pooled estimate for the difference in 48 hour serum creatinine concentrations between the theophylline and control groups was −15.2 μmol/l (95% CI −24.6 to −5.7 μmol/l) ($p = 0.002$), indicating that theophylline may be protective in CIN. CIN requiring dialysis was uncommon and reported in only one case.

▲ Bagshaw SM, Ghali WA. Theophylline for prevention of contrast-induced nephropathy: a systematic review and meta-analysis. *Arch Intern Med* 2005;**165**:1087–93.

Bezafibrate has some mortality data in coronary heart disease ► A consistent relation between metabolic syndrome (MS) and myocardial infarction (MI) has been demonstrated. The effect of bezafibrate retard, a fibric acid derivative, on the incidence of MI in patients with MS enrolled in the bezafibrate infarction prevention (BIP) study was assessed. Patients who displayed at least three of the following five risk factors were considered to have MS: (1) a fasting glucose concentration of 110 mg/dl (6.11 mmol/l); (2) a triglyceride concentration of 150 mg/dl (1.70 mmol/l); (3) a high density lipoprotein cholesterol concentration < 40 mg/dl (< 1.04 mmol/l) in men or < 50 mg/dl (<1.30 mmol/l) in women; (4) a systolic blood pressure of 130 mm Hg or diastolic blood pressure of 85 mm Hg; and (5) a body mass index of 28.0 kg/m^2. The study sample for this post hoc subgroup analyses comprised 1470 patients aged 42–74 years. The patients received either 400 mg of bezafibrate retard (740 patients) or placebo (730 patients) once a day. The mean follow up period was 6.2 years for events and 8.1 years for mortality data. New MI was recorded in 193 patients: 82 (11.1%) of the 740 patients in the bezafibrate group versus 111 (15.2%) of the 730 patients in the placebo group ($p = 0.02$). Bezafibrate was associated with a reduced risk of any MI and non-fatal MI with hazard ratios of 0.71 (95% CI 0.54 to 0.95) and 0.67 (95% CI 0.49 to 0.91), respectively. The cardiac mortality risk tended to be lower in patients taking bezafibrate (HR 0.74, 95% CI 0.54 to 1.03). In 575 patients with augmented features of MS (4–5 risk factors), the remarkable strengthening of cardiac mortality reduction when taking bezafibrate (HR 0.44, 95% CI 0.25 to 0.80) should be noted. This would still not force the clinician to forgo statins as first line risk reduction treatment, but strengthens the case for bezafibrate in statin intolerant cases.

▲ Tenenbaum A, Motro M, Fisman EZ, *et al*. Bezafibrate for the secondary prevention of myocardial infarction in patients with metabolic syndrome. *Arch Intern Med* 2005;**165**:1154–60.

CT scanning to replace coronary angiography? ► Recent evolution of multislice computed tomography (MSCT) scanner technology now allows non-invasive imaging of the coronary tree within a single breath hold of less than 25 seconds; but how accurate are the images obtained when compared to the gold standard of coronary angiography? Hoffman and colleagues took 103 patients with a suspected diagnosis of coronary artery disease who had been referred for angiography and also performed MSCT scans. Compared with coronary angiography for the detection of significant lesions ($> 50\%$ stenosis), segment based sensitivity, specificity, and positive and negative predictive values were 95%, 98%, 87%, and 99%, respectively. Threshold optimisation allowed 100% detection of patients who could be candidates for revascularisation ($> 50\%$ left main artery stenosis, and/or $> 70\%$ stenosis in any other epicardial vessel), at reasonable false positive rate (specificity 76.5%). Non-diagnostic image quality was obtained from only 88 of 1384 segments scanned (6.4%), mainly due to faster heart rates. However, the appropriate role of this new imaging technique in clinical practice remains to be established.

▲ Hoffman MHK, Shi H, Schmitz HS, *et al*. Noninvasive coronary angiography with multislice computed tomography. *JAMA* 2005;**293**:2471–8.

Risk factors for stent thrombosis in drug eluting stents ► Iakovou and colleagues followed 2229 patients treated with sirolimus eluting (1062 patients) or paclitaxel eluting (1167 patients) stents for an average of nine months. Those suffering an MI less than

48 hours before the procedure, or who had intraprocedural stent thrombosis, were excluded. At nine month follow up, 29 patients (1.3%) had stent thrombosis (9 (0.8%) with sirolimus and 20 (1.7%) with paclitaxel; p = 0.09). Fourteen patients had subacute thrombosis (0.6%) and 15 patients had late thrombosis (0.7%). Independent predictors of stent thrombosis were premature antiplatelet treatment discontinuation, renal failure, bifurcation lesions, diabetes, and lower ejection fraction. The authors note that their figure of 1.3% is substantially higher than the rates reported in major clinical trials (0.4% at one year for sirolimus and 0.6% at nine months for paclitaxel).

▲ Iakovou I, Schmidt T, Bonizzoni E, *et al*. Incidence, predictors, and outcome of thrombosis after succesful implantation of drug-eluting stents. *JAMA* 2005;**293**:2126–30.

GENERAL CARDIOLOGY

Lipid lowering for aortic stenosis: stopped before it began? ► Small studies suggested that calcific aortic stenosis (AS) had similar risk factors to atherosclerosis. Retrospective studies suggested that progression of valve gradient rise and calcification may be slowed by statin treatment. The Scottish aortic stenosis and lipid lowering trial, impact on regression (SALTIRE) was to establish whether intensive lipid lowering treatment with 80 mg of atorvastatin daily would halt the progression of AS. Of 455 eligible patients, 155 were randomised to atorvastatin versus placebo. Peak velocity of 2.5–4 m/s were included in the study. Increases in aortic jet velocity were 0.199 (0.210) m/s per year in the atorvastatin group and 0.203 (0.208) m/s per year in the placebo group (p = 0.95; adjusted mean difference 0.002, 95% CI −0.066 to 0.070 m/s per year). Progression in valvar calcification was 22.3 (21.0)% per year in the atorvastatin group, and 21.7 (19.8)% per year in the placebo group (p = 0.93; ratio of post-treatment aortic valve calcium score 0.998, 95% CI 0.947 to 1.050). Thus atorvastatin does not seem to stop the progression of AS in a clinically at risk population.

▲ Cowell SJ, Newby DE, Prescott RJ, *et al*, for the Scottish Aortic Stenosis and Lipid Lowering Trial, Impact on Regression (SALTIRE) Investigators. A randomized trial of intensive lipid-lowering therapy in calcific aortic stenosis. *N Engl J Med* 2005;**352**:2389–97.

ACE inhibitors may reduce progression of calcification in aortic valves ► An association between angiotensin converting enzyme (ACE) inhibitor use and lowered aortic valve calcium (AVC) accumulation, as measured by electron beam computed tomography (EBCT), was assessed. Rates of change in volumetric AVC scores were determined retrospectively for 123 patients who had undergone two serial EBCT scans. The mean (SD) interscan interval was 2.5 (1.7) years; 80 patients did not receive ACE inhibitors and 43 did. Unadjusted and adjusted (for coronary heart disease risk factors and baseline calcium score) median rates of AVC score change were significantly higher in the non-ACE inhibitor group than in the ACE inhibitor group (adjusted median AVC changes: relative, 28.7%/y (95% CI 18.9%/y to 38.5%/y) *v* 11.0%/y (95% CI −1.9%/y to 24.0%/y), p = 0.04; absolute: 25.1/y (95% CI 19.7/y to 30.5/y) *v* 12.2/y (95% CI 4.5/y to 19.9/y), p = 0.02). The adjusted odds ratio for definite AVC progression was significantly lower for patients who received ACE inhibitors (OR 0.29, 95% CI 0.11 to 0.75, p = 0.01). This retrospective study finds a significant association between ACE inhibitor use and a lower rate of AVC accumulation. The results support the need for prospective, randomised trials of ACE inhibitors in calcific aortic valve disease.

▲ O'Brien KD, Probstfield JL, Caulfield MT, *et al*. Angiotensin-converting enzyme inhibitors and change in aortic valve calcium. *Arch Intern Med* 2005;**165**:858–62.

Statins reduce risk of colon cancer ► Statins are inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A reductase and effective lipid lowering agents. Statins inhibit the growth of colon cancer cell lines, and secondary analyses of some, but not all, clinical trials suggest that they reduce the risk of colorectal cancer. The molecular epidemiology of colorectal cancer study was a population based case–control study of patients who received a diagnosis of colorectal cancer in northern Israel between 1998 and 2004 and controls, matched according to age, sex, clinic, and ethnic group. In analyses including 1953 patients with colorectal cancer and 2015 controls, the use of statins for at least five years (versus the non-use of statins) was associated with a significantly reduced relative risk of colorectal cancer (OR 0.50, 95% 0.40 to 0.63). This association remained significant after adjustment for the use or non-use of aspirin or other non-steroidal anti-inflammatory drugs; the presence or absence of physical activity, hypercholesterolaemia, and a family history of colorectal cancer; ethnic group; and level of vegetable consumption (OR 0.53, 95% CI 0.38 to 0.74). The use of fibric acid derivatives was not associated with a significantly reduced risk of colorectal cancer (OR 1.08, 95% 0.59 to 2.01). Self reported statin use was confirmed for 276 of the 286 participants (96.5%) who reported using statins and whose records were available. The number of lives saved is small, however, and cost effectiveness needs to be assessed if this indication is to be validated.

▲ Poynter JN, Gruber SB, Higgins PDR, *et al*. Statins and the risk of colorectal cancer. *N Engl J Med* 2005;**352**:2184–92.

Cystatin C as a marker of risk in elderly patients ► Cystatin C is a non-glycosylated 13 000 dalton basic protein that is filtered by the glomeruli and reabsorbed and catabolised by the tubular epithelial cells, with only small amounts excreted in the urine. Cystatin C was a strong and independent predictor of overall mortality and mortality from cardiovascular causes in a population based cohort of ambulatory elderly persons followed for 10 years. In this study, the cystatin C concentration had a strong, direct correlation with the creatinine concentration ($r = 0.79$, $p < 0.001$) and an inverse correlation with the estimated glomerular filtration rate (GFR) ($r = -0.63$, $p < 0.001$). Using cut-off points at the 40th and 80th centiles of cystatin C, groups at low, intermediate, and high risk with respect to death from all causes and from cardiovascular causes (cystatin C concentrations: < 1.00, 1.00–1.28, and ⩾ 1.29 mg/l, respectively) were found. As compared with the two lowest quintiles combined (cystatin C ⩽ 0.99 mg/l), the highest quintile of cystatin C (⩾ 1.29 mg/l) was associated with a significantly increased risk of death from cardiovascular causes (HR 2.27, 95% CI 1.73 to 2.97), MI (HR 1.48, 95% CI 1.08 to 2.02), and stroke (HR 1.47, 95% CI 1.09 to 1.96) after multivariate adjustment. High cystatin C concentrations were also independently associated with the risk for newly diagnosed MI and stroke. The cystatin C concentration appeared to provide a stronger estimate of the risk of cardiovascular events and death among elderly persons than either the creatinine value or the estimated GFR. The insensitivity of creatinine and estimated GFR values for detecting renal dysfunction has limited their value as prognostic factors. This study suggests the linear increase in risk was observed only among participants with creatinine concentrations of > 115 μmol/l—the upper 14% of the cohort. Whether measurement of cystatin C will alter clinical decisions is not yet clear.

▲ Shlipak MG, Sarnak MJ, Katz RF, *et al*. Cystatin C and the risk of death and cardiovascular events among elderly persons. *N Engl J Med* 2005;**352**:2049–60.

Exercise responses predict long term survival ► Alterations in the neural control of cardiac function contribute to the risk of sudden death. A total of 5713 asymptomatic working men (between 42–53 years old), none of whom had clinically detectable cardiovascular disease, underwent standardised graded exercise testing between 1967 and 1972. Data on the subjects' resting heart rates, the increase in rate from the resting level to the peak exercise level, and the decrease in rate from the peak exercise level to the level one minute after the termination of exercise were reviewed. During a 23 year follow up period, 81 subjects died suddenly. The risk of sudden death from myocardial infarction was increased in subjects with a resting heart rate that was more than 75 beats/min (relative risk (RR) 3.92, 95% CI 1.91 to 8.00); in subjects with an increase in heart rate during exercise that was less than 89 beats/min (RR 6.18, 95% CI 2.37 to 16.11); and in subjects with a decrease in heart rate of less than 25 beats/min after the termination of exercise (RR 2.20, 95% CI 1.02 to 4.74). After adjustment for potential confounding variables, these three factors remained strongly associated with an increased risk of sudden death, with a moderate but significantly increased risk of death from any cause but not of non-sudden death from myocardial infarction. These measures may just reflect poor physical condition and thus overall health, even in apparently ''healthy'' individuals.

▲ Jouven X, Empana J-P, Schwartz PJ, *et al*. Heart-rate profile during exercise as a predictor of sudden death. *N Engl J Med* 2005;**352**:1951–8.

S3 and S4 linked to physiology ► This paper examines the link between phonographic third and fourth heart sounds and the

diagnostic test characteristics for detection of left ventricular dysfunction. The mean age of the 90 patients studied was 62 years and 68% were male. Overall, those with an S3 or S4, when compared to those with no diastolic heart sounds, showed higher left ventricular end diastolic pressures (LVEDPs) (18.4 mm Hg *v* 12.1 mm Hg), lower left ventricular ejection fractions (LVEFs) (49.4% *v* 63.6%), and raised B type natriuretic peptide (BNP) (330 pg/ml *v* 86 pg/ml). However, the sensitivities of these heart sounds to detect raised LVEDP, reduced LVEF, or raised BNP were 41%, 52%, and 32% for an S3, and 46%, 43%, and 40% for an S4, respectively. The specificities of S3 were 92%, 87%, and 92%, while the specificities of S4 were 80%, 72%, and 78%, respectively. Therefore, although neither phonocardiographic S3 or S4 are sensitive markers of left ventricular dysfunction, phonocardiographic S3 is fairly specific for left ventricular dysfunction, certainly more so than S4.

▲ Marcus GM, Gerber IL, McKeown BH, *et al*. Association between phonocardiographic third and fourth heart sounds and objective measures of left ventricular function. *JAMA* 2005;**293**:2238–44.

Journals scanned

American Journal of Medicine; American Journal of Physiology: Heart and Circulatory Physiology; Annals of Emergency Medicine; Annals of Thoracic Surgery; Archives of Internal Medicine; BMJ; Chest; European Journal of Cardiothoracic Surgery; Lancet; JAMA; Journal of Clinical Investigation; Journal of Diabetes and its Complications; Journal of Immunology; Journal of Thoracic and Cardiovascular Surgery; Nature Medicine; New England Journal of Medicine; Pharmacoeconomics; Thorax

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IMAGES IN CARDIOLOGY

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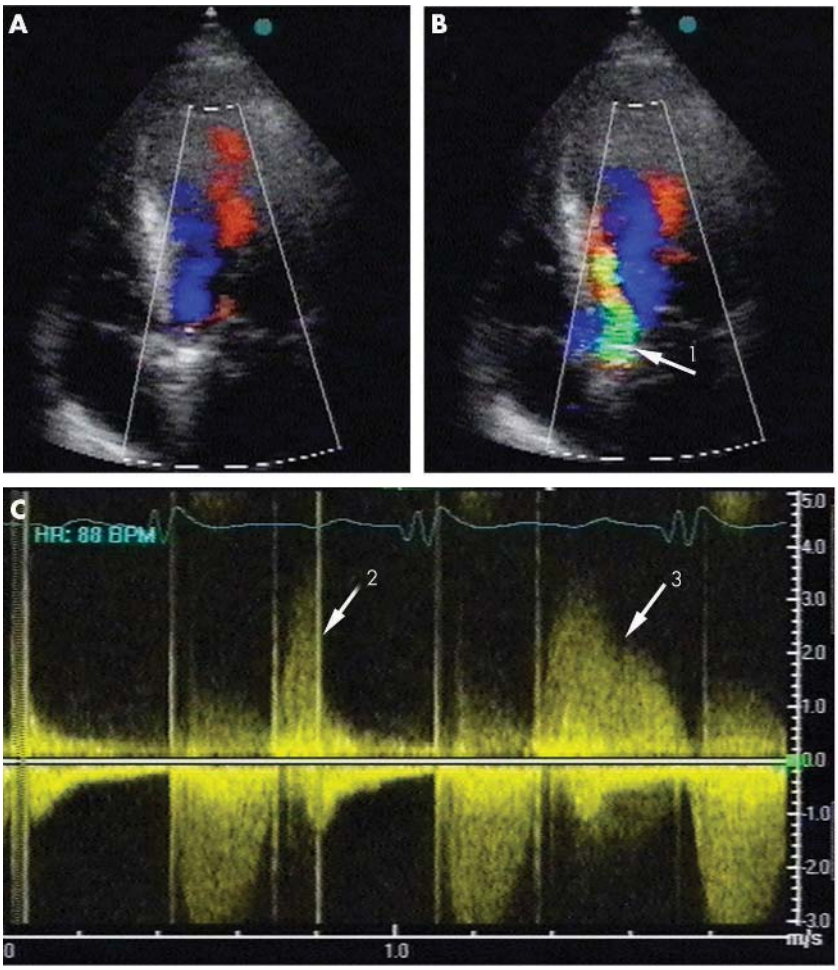
Dysfunction of an aortic prosthetic valve

A 64 year old man had received a Medtronic-Hall aortic valve prosthesis eight years previously. During follow up the systolic gradient across the valve prosthesis had increased from 32 to 68 mm Hg without symptoms. He was now admitted with acute shortness of breath. On admission he was dyspnoeic, his pulse was 68 per minute and regular, and his blood pressure was 100/60 mm Hg. The clicks of the prosthetic valve were normal, and a systolic ejection murmur was unchanged. Intermittently the murmur of aortic insufficiency was heard. The ECG showed sinus rhythm and a left bundle branch block, unchanged from previous tracings. A therapeutic international normalised ratio (INR) of 3.9 was documented. Doppler echocardiography showed beats without aortic insufficiency (panel A) and intermittent beats with severe aortic insufficiency (panel B, arrow 1). The continuous wave recording (panel C) showed beats in which initial aortic insufficiency was seen, abruptly interrupted by a click (arrow 2) and beats with holodiastolic aortic insufficiency (arrow 3). The diagnosis of valve obstruction caused by pannus formation and intermittent regurgitation from impaired valve closure was confirmed during surgery. The valve was replaced. Pathologic examination of the specimen showed mixed fibrotic tissue and organised thrombus. The patient recovered well from surgery.



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